Sinus surgery and delivery method influence the effectiveness of topical corticosteroids for chronic rhinosinusitis: Systematic review and meta-analysis

Kornkiat Snidvongs, M.D.,[1,2] Larry Kalish, M.D., M. Med. (Clin Epi),[3,4] Raymond Sacks, M.D.,[1,3,4] Rahuram Sivasubramaniam, M.D.,[5] Daron Cope, M.D.,[6] and Richard J Harvey, M.D.[1,6,7]

ABSTRACT

Background: *Published randomized controlled trials (RCTs) on the efficacy of intranasal corticosteroid (INCS) in chronic rhinosinusitis (CRS) use either nasal delivery (nasal drop or nasal spray) or sinus delivery (sinus catheter or sinus irrigation) in patients with or without sinus surgery. This influences topical drug delivery and distribution. The effect of these factors on the published results of RCTs is assessed. This systematic review explores the strength of evidence supporting the influence of sinus surgery and delivery methods on the effectiveness of topical steroids in studies for CRS with meta-analyses.*

Methods: *A systematic review was conducted of RCTs comparing INCS with either placebo or no intervention for treating CRS. Data were extracted for meta-analysis and subgroup analyses by sinus surgery status and topical delivery methods.*

Results: *Forty-eight studies (3961 patients) met the inclusion criteria. INCS improved overall symptoms (standardized mean difference [SMD], −0.49; $p < 0.00001$) and the proportion of responders (risk ratio [RR], 0.59; $p < 0.00001$) compared with placebo. It decreased nasal polyp size with a greater proportion of responders (RR, 0.48; $p < 0.00001$) and prevented polyp recurrence (RR, 0.59; $p = 0.0004$) compared with placebo. Reduction of polyp size was greater in patients with sinus surgery (RR, 0.31; 95% confidence interval [CI], 0.20, 0.48) than those without (RR, 0.61; 95% CI, 0.46, 0.81; $p = 0.009$). Greater symptom improvement occurred when sinus delivery methods (SMD, −1.32; 95% CI, −2.26, −0.38) were compared with nasal delivery methods (SMD, −0.38; 95% CI, −0.55, −0.22; $p < 0.00001$).*

Conclusion: *INCS is effective for CRS. Prior sinus surgery and direct sinus delivery enhance the effectiveness of INCS in CRS.*

(Am J Rhinol Allergy 27, 221–233, 2013; doi: 10.2500/ajra.2013.27.3880)

Inflammatory dysfunction is considered an important part of chronic rhinosinusitis (CRS). Anti-inflammatory therapy, including corticosteroid,[1] doxycycline,[2] and low-dose macrolides,[3] plays a significant role in the treatment of CRS. Compared with oral corticosteroid administration, topical corticosteroids are more widely used as a treatment because they can be given for longer periods without the associated systemic side effects and potentially achieve better drug concentration in the sinus mucosa.

However, simply applying topical steroid through the nostrils does not imply delivery of the drug into the sinus. To deliver topical medicine into the sinuses, an appropriate access and delivery is required. Sinus surgery greatly affects the amount of corticosteroid, which comes into contact with paranasal sinus mucosa.[4–6] The edematous inflammatory mucosa and ostiomeatal occlusion often seen in CRS allows <1% of solution volume to enter the sinus cavities before surgery.[7] The extent of sinus surgery varies across institutions. This difference brings about variable access and sinus penetration. An adequate ostial dimension has been shown to be necessary for appropriate topical drug distribution.[4,8–10] Additionally, an appropriate device and delivery technique is required for adequate administration.[4,8] Simple nasal delivery methods such as drops, sprays, aerosols, nebulizers, and atomizers provide good nasal cavity contact but poor sinus delivery. Nasal irrigation, with squeeze bottles and NETI pots, along with direct sinus cannulation, are likely to provide better delivery to the sinuses, especially in the post–sinus surgery setting.[4,5]

Studies investigating topical steroid for CRS have a high level of heterogeneity, and systematic reviews[11–13] rarely discuss or explore this heterogeneity of patient groups and outcomes. Trials studying the effectiveness of topical corticosteroid used various topical delivery methods and patients with both nonsurgical and post–endoscopic sinus surgery (ESS) cavities. This systematic review aims to assess the strength of evidence supporting the influence of sinus surgery and delivery methods on the benefit of topical steroids in CRS.

From [1]Australian School of Advanced Medicine, Macquarie University, Sydney, Australia, [2]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [3]Sydney Medical School, University of Sydney, Sydney, Australia, [4]Department of Otolaryngology, Concord General Hospital, Concord, New South Wales, Australia, [5]Department of Otolaryngology, Canberra Hospital, Garran, Australian Capitol Territory, Australia, [6]Department of Otolaryngology-Head and Neck, Skull Base Surgery, St Vincent's Hospital, Sydney, Australia, and [7]St Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, Australia

L Kalish is on the speaker bureau for Merek Sharp Dolme (MSD), Takeda and Care Pharmaceuticals. R Sacks is consultant for Medtronic and Nycomed, speakers' bureau for Merek Sharp Dolme and Arthrocare. RJ Harvey, has served on an advisory board for Schering-Plough and GlaxoSmithKline, previous consultant with Medtronic, Olympus, speakers' bureau for Merek Sharp Dolme and Arthrocare and has received grant support from NeliMed. The remaining authors have no conflicts of interest to declare pertaining to this article

Address correspondence and reprint requests to Kornkiat Snidvongs, M.D., The Australian School of Advanced Medicine, 2 Technology Place, Macquarie University NSW 2109, Australia

E-mail address: drkornkiat@yahoo.com

MATERIALS AND METHODS

Search Methods for Identification of Studies

Electronic systematic searches for randomized controlled trials (RCTs) were conducted with no language, publication year, or publication status restrictions. A search strategy was used with a combination of MESH terms and key words in collaboration with the Cochrane Ear, Nose, and Throat disorders group. The Cochrane Ear, Nose, and Throat Disorders group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT; and additional sources were searched for published and unpublished trials. The date of the last search was April 10, 2012.

Criteria for Included Studies

Types of Studies. RCTs, which fulfilled the criteria described previously, were included.

Types of Participants. Both adults and children with CRS as defined by either European Position Paper on Rhinosinusitis and Nasal Pol-

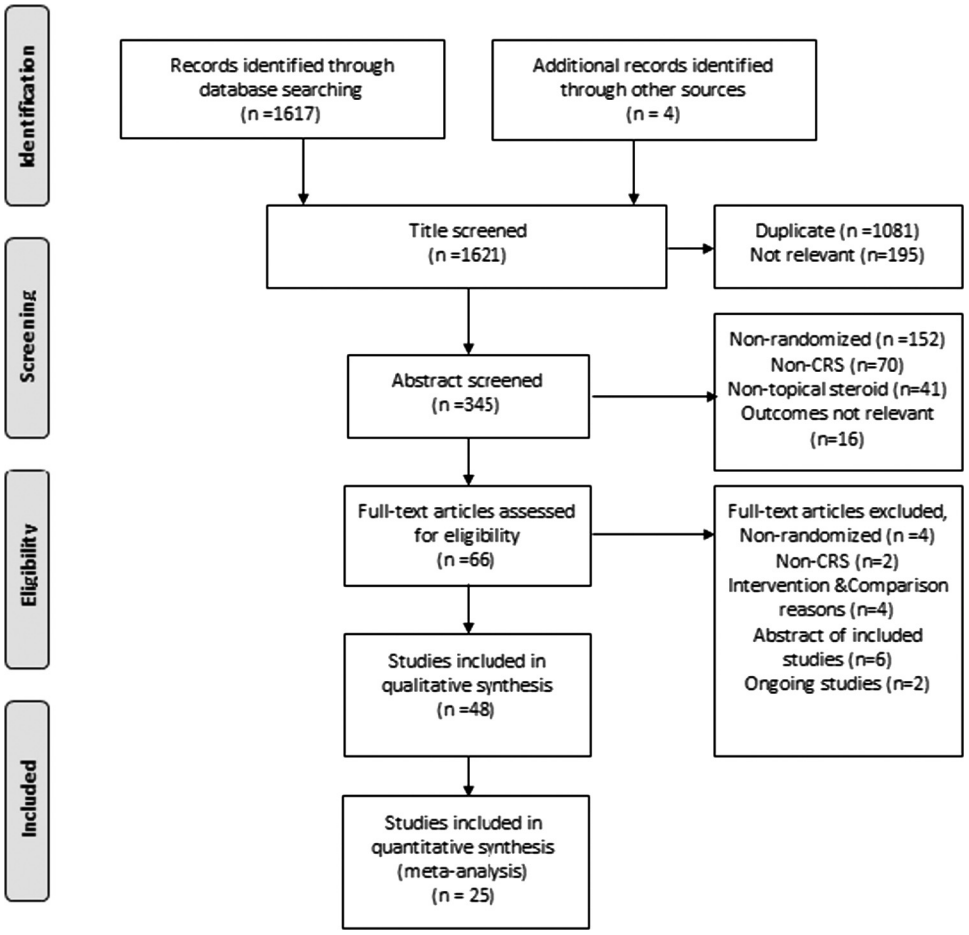

Figure 1. *Flowchart of study retrieval and selection on topical steroid for chronic rhinosinusitis (CRS).*

yps 2007[14] or Rhinosinusitis Task Force Report[15] and its revision[16] were included; all candidates had chronic sinonasal symptoms for >12 weeks. Antrochoanal polyps, cystic fibrosis, and primary ciliary dyskinesia were excluded.

Types of Interventions. Studies involving topical steroid therapies versus either placebo or no treatment were considered. Trials using any cointerventions including oral steroid, antihistamines, decongestants, and antibiotics (topical or i.v.) were included when the cointerventions were equally applied in both groups.

Types of Outcome Measures. The outcomes were sinonasal symptoms, polyp size, polyp recurrence, and adverse effects.

Statistical Analysis

Data Synthesis. Comparable data were combined to give a summary measure of effect. The standardized mean difference (SMD) and 95% confidence intervals (CIs) were used for continuous data. The risk ratio (RR) and 95% CIs were used for dichotomous data. A fixed-effect model was used. Statistical assessments were performed using Review Manager (RevMan) Version 5.1.6 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The I^2 of <40%, 40–60%, and >60% represent low, moderate, and substantial heterogeneity.

Subgroup Analysis. When heterogeneity was present, subgroup analysis was performed for sinus surgery status (patients with sinus surgery versus without sinus surgery) and topical delivery methods (sinus delivery such as direct cannulation and irrigation postsurgery versus nasal delivery such as sprays, drops, and nebulizers). We investigated differences between the two subgroups for fixed-effect analyses based on the inverse variance method in the case of continuous data and the Mantel-Haenszel method in the case of dichotomous data.

Dealing with Missing Data. The study authors were contacted *via* e-mail for raw data in cases of missing data.[17–30] The analyses were based on intention to treat. For missing standard deviations, either 95% CIs,[23,31,32] standard error.[19,21,33–37] *p* value,[26] range,[20] or interquartile ranges[18,20] was used for estimation to impute standard deviations. For missing means, medians were converted.[18,20] The correlation coefficient was calculated in the experimental and control groups from some studies[38,39] and was used to calculate the imputation of standard deviation of change in symptom scores for other studies.[18,34–36]

RESULTS

Results of the Search

A total of 1537 references were identified. Four more records were identified from the references of these studies. Twelve hundred seventy-six of these were excluded after screening the title, 279 studies were removed after abstract were analyzed, and 18 additional studies were removed after full text assessment, leaving 48 studies included. A flowchart of study retrieval and selection is displayed in Fig. 1.

Included Studies

There were 48 studies fulfilling the inclusion criteria for trials of topical steroid for CRS. Forty-two (87.5%) trials compared topical steroid against placebo.[17–20,22–59] Five trials (10.4%) compared topical steroid against no intervention.[60–64] One trial (2.1%) compared two different treatment regimens for steroid administration.[65] The characteristics of the included studies are displayed in Table 1.

Table 1 **Study characteristics of included studies on topical steroid for CRS**

Study	Study Type	Participants (diagnostic criteria)	No. of Participants	Age (yr; mean)	Type of Steroid	Steroid Dose	Sinus Surgery Status	Delivery Method of Steroid	Duration of Treatment (wk)	Comparison
Vento 2012[58]	RCT	CRSwNP (NS)	60	51.4	Triamcinolone acetonide	220 μg o.d.	With sinus surgery	Aerosol	36	Placebo
Rotenberg 2011[63]	RCT	CRSwNP (Samter's triad)	64	47.5	Budesonide	Arm 1 (spray), 128 μg b.i.d.; Arm 2, (irrigation) 500 μg b.i.d.	With sinus surgery	Spray and nasal irrigation	52	No treatment
Chur 2010 [28]	RCT	CRSwNP (NS)	127	NS	Mometasone furoate	100 μg (aged 6–11 yr) 200 μg (aged 12–17 yr) Arm 1 o.d.; Arm 2 b.i.d.	Without sinus surgery	Spray	16	Placebo
Olsson 2010[47]	RCT	CRSwNP (by endoscopy)	68	51.6	Fluticasone propionate	400 μg b.i.d.	With sinus surgery	Nasal drop	10	Placebo
Ehnhage 2009[31]	RCT	CRSwNP (by endoscopy)	68	51.6	Fluticasone propionate	400 μg bid	With sinus surgery	Nasal drop	10	Placebo
Jankowski 2009[(38)]	RCT	CRSwNP (by endoscopy)	242	51	Fluticasone propionate	200 μg b.i.d.	Without sinus surgery	Spray	4	Placebo
Jorissen 2009[24]	RCT	Mixed CRS (by endoscopy)	99	47.4	Mometasone furoate	200 μg b.i.d.	With sinus surgery	Spray	24	Placebo
Stjarne 2009[57]	RCT	CRSwNP (by endoscopy)	159	48.5	Mometasone furoate	200 μg o.d.	With sinus surgery	Spray	24	Placebo
Vlckova 2009[54]	RCT	CRSwNP, small-to-medium size (by endoscopy)	109	47.9	Fluticasone propionate	400 μg b.i.d.	With sinus surgery	Spray	12	Placebo
Stjarne 2006[55]	RCT	CRSwNP (by endoscopy)	310	48.6	Mometasone furoate	Arm 1, 200 μg o.d.; Arm 2, 200 μg b.i.d.	Without sinus surgery	Spray	16	Placebo
Stjarne 2006b[56]	RCT	CRSwNP (by endoscopy)	298	53	Mometasone furoate	200 μg o.d.	Without sinus surgery	Spray	16	Placebo
Aukema 2005[25]	RCT	CRSwNP (by endoscopy and CT)	54	44	Fluticasone propionate	400 μg o.d.	With sinus surgery	Nasal drop	12	Placebo
Furukido 2005[17]	RCT	CRSsNP (by AAO-HNS)	25	53.7	Betamethasone	2-mL solution (0.4 mg/ml) weekly	Without sinus surgery	Through YAMIK nasal catheter	4	Placebo
Rowe-Jones 2005[50]	RCT	CRSwNP (by endoscopy)	109	41	Fluticasone propionate	200 μg b.i.d.	With sinus surgery	Spray	260	Placebo
Small 2005[(52)]	RCT	CRSwNP (by endoscopy)	354	47.5	Mometasone furoate	Arm 1, 200 μg o.d.; arm 2, 200 μg b.i.d.	Without sinus surgery	Spray	16	Placebo

Table 1 **Continued**

Study	Study Type	Participants (diagnostic criteria)	No. of Participants	Age (yr; mean)	Type of Steroid	Steroid Dose	Sinus Surgery Status	Delivery Method of Steroid	Duration of Treatment (wk)	Comparison
Bross-Soriano 2004[26]	RCT	CRSwNP (NS)	142	40.4	Arm1.fluticasone propionate Arm2. beclomethasone dipropionate	Arm 1., fluticasone propionate, 400 μg o.d.; Arm 2, beclomethasone dipropionate, 600 μg o.d.	With sinus surgery	Spray (after saline lavage)	72	Saline lavage only
Dijkstra 2004[23]	RCT	Mixed CRS (by endoscopy and CT)	162	41	Fluticasone propionate	Arm 1, 400 μg b.i.d.; Arm 2, 800 μg b.i.d.	With sinus surgery	spray	52	Placebo
Jurkiewickz 2004[60]	RCT	CRSwNP (NS)	86	NS	Fluticasone propionate	400 μg b.i.d.	With sinus surgery	Spray	52	No treatment
Lund 2004[19]	RCT	CRSsNP (by symptoms)	167	40.6	Budesonide	128 μg b.i.d.	Undefined	Spray	20	Placebo
Giger 2003[64]	RCT	allergic rhinitis or CRSsNP (by symptoms)	112	32.3	Beclomethasone dipropionate	200 μg b.i.d.	Without sinus surgery	Spray	12	Beclomethasone dipropionate 400 μg o.d.
Passali 2003[48]	RCT	CRSwNP, medium to large size (by endoscopy)	73	37.3	Mometasone furoate	400 μg o.d.	With sinus surgery	Spray	52 (at least)	1. Placebo; 2. intranasal furosemide
Johansson 2002[40]	RCT	CRSwNP (by endoscopy)	98	56	Budesonide	128 μg b.i.d.	Without sinus surgery	Spray	2	Placebo
Lavigne 2002[18]	RCT	CRSsNP (by symptoms)	26	46	Budesonide	2 mL solution (256 μg) o.d.	With sinus surgery	Through maxillary sinus catheter	3	Placebo
Jankowski 2001[37]	RCT	CRSwNP (by endoscopy)	183	44	Budesonide	Arm 1, 128 μg o.d.; Arm 2, 128 μg b.i.d.; Arm 3, 256 μg o.d.	Without sinus surgery	Spray	8	Placebo
Parikh 2001[21]	RCT	CRSsNP (by symptoms, endoscopy and CT)	29	46.6	Fluticasone propionate	200 μg b.i.d.	Undefined	Spray	16	Placebo
Filiaci 2000[32]	RCT	CRSwNP (by endoscopy and MRI)	157	47.9	Budesonide	Arm 1, 140 μg b.i.d.; Arm 2, 280 μg o.d; Arm 3, 140 μg o.d.	Without sinus surgery	Turbuhaler	8	Placebo
Keith 2000[41]	RCT	CRSwNP, small to medium size (by endoscopy)	104	48	Fluticasone propionate	400 μg o.d.	With sinus surgery	Nasal drop	12	Placebo

Table 1 **Continued**

Study	Study Type	Participants (diagnostic criteria)	No. of Participants	Age (yr; mean)	Type of Steroid	Steroid Dose	Sinus Surgery Status	Delivery Method of Steroid	Duration of Treatment (wk)	Comparison
Pentilla 2000[49]	RCT	CRSwNP, small to medium size (by endoscopy)	142	51	Fluticasone propionate	Arm 1, 400 μg b.i.d.; Arm 2, 400 μg o.d.	With sinus surgery	Nasal drop	12	Placebo
Holmstrom 1999[35]*	RCT	CRSwNP, small to medium size (by endoscopy)	104	NS	Fluticasone propionate	400 μg o.d.	Without sinus surgery	Nasal drop	12	Placebo
Lund 1998[44]	RCT	CRSwNP (by endoscopy and CT)	29	49.3	1. Fluticasone propionate; 2. beclomethasone dipropionate	Arm 1, fluticasone propionate 400 μg b.i.d.; Arm 2, beclomethasone 400 μg b.i.d.	With sinus surgery	Spray	12	Placebo
Tos 1998[53]	RCT	CRSwNP, medium to large size (by endoscopy)	138	NS	Budesonide	Arm 1, spray 64 μg b.i.d.; Arm 2, Turbuhaler 100 μg/ nominal dose/ 170 μg per delivered dose b.i.d.	With sinus surgery	Spray or turbuhaler	6	Placebo
Holmberg 1997[34]	RCT	CRSwNP (by endoscopy)	55	54	Arm1, fluticasone propionate ; Arm 2, beclomethasone dipropionate	Arm 1, fluticasone propionate 200 μg b.i.d.; Arm 2, beclomethasone dipropionate 200 μg b.i.d.	With sinus surgery	Spray	26	Placebo
Mastalerz 1997[45]	RCT crossover	Mixed CRS, with aspirin sensitivity (NS)	15	44.7	Fluticasone propionate	400 μg o.d.	Without sinus surgery	Spray	4	Placebo
El Naggar1995[59]	RCT	CRSwNP (by endoscopy)	29	51.5	Beclomethasone dipropionate	100 μg b.i.d. in one nostril	With sinus surgery	Spray	6	No treatment in the other nostril
Lildholdt 1995[43]	RCT	CRSwNP (by rhinoscopy)	126	51	Budesonide	Arm1, 200 μg; Arm 2, 400 μg b.i.d.	Without sinus surgery	Turbuhaler	4	placebo

Table 1 **Continued**

Study	Study Type	Participants (diagnostic criteria)	No. of Participants	Age (yr; mean)	Type of Steroid	Steroid Dose	Sinus Surgery Status	Delivery Method of Steroid	Duration of Treatment (wk)	Comparison
Johansen 1993[39]	RCT	CRSwNP, small to medium size eosinophilic polyps (by pathology)	91	52	Budesonide	200 μg b.i.d.	Without sinus surgery	Spray and aerosol	12	Placebo
Qvarnberg 1992[22]	RCT	CRSsNP (by symptoms)	40	45.4	Budesonide	200 μg b.i.d.	Without sinus surgery	Aerosol	12	Placebo
Ruhno 1990[51]	RCT	CRSwNP (NS)	36	46.6	Budesonide	400 μg b.i.d.	With sinus surgery	Spray	4	Placebo
Hartwig 1988[33]	RCT	CRSwNP (by endoscopy)	73	54.2	Budesonide	200 μg b.i.d.	With sinus surgery	Aerosol	24	Placebo
Cuenant 1986[62]	RCT	CRSsNP (by symptoms, endoscopy, radiograph and ventilometry)	60	39	Tixocortol pivalate	5 mL Solution of 50 mg	Without sinus surgery	Through maxillary sinus catheter (plus neomycin)	11/7	Neomycin only
Sykes 1986[20]	RCT	CRSsNP (by symptoms)	50	not stated	Dexamethasone	20 μg o.d.	Without sinus surgery	Spray	2	Placebo
Chalton 1985[27]	RCT	CRSwNP (by endoscopy)	30	42	Betamethasone	100 μg b.i.d.	Without sinus surgery	Nasal drop	4	Placebo
Dingsor 1985[29]	RCT	CRSwNP (by rhinoscopy)	41	49	Flunisolide	100 μg b.i.d.	With sinus surgery	Spray	52	Placebo
Lang 1983[42]	RCT	CRSwNP, small to medium size (by endoscopy)	32	42	Beclomethasone dipropionate	400 μg b.i.d.	Without sinus surgery	Spray	104	Placebo
Drettner 1982[30]	RCT	CRSwNP (NS)	25	43.8	Flunisolide	100 μg b.i.d.	With sinus surgery	Spray	12	Placebo
Holopainen 1982[36]	RCT	CRSwNP, small to medium size (by rhinoscopy)	19	42	Budesonide	200 μg b.i.d.	With sinus surgery	Spray	16	Placebo
Karlsson 1982[61]	RCT	CRSwNP, medium to large size (NS)	40	49	Beclomethasone dipropionate	400 μg o.d. for1 mo and then 200 μg o.d.	With sinus surgery	Intranasal	30	No treatment
Mygind 1975[46]	RCT	CRSwNP, medium to large size (NS)	35	51	beclomethasone dipropionate	100 μg q.i.d.	With sinus surgery	Aerosol	3	Placebo

**There are two studies in this article. Data from study 1 were presented under Holmstrom 1999. Data from study 2 were presented under Pentilla 2000.*
CRSwNP = chronic rhinosinusitis with nasal polyps; CRSsNP = chronic rhinosinusitis without nasal polyps; NS = not stated; RCT = randomized controlled trial; o.d. = once daily; b.i.d. = twice daily; q.i.d. = four times daily.

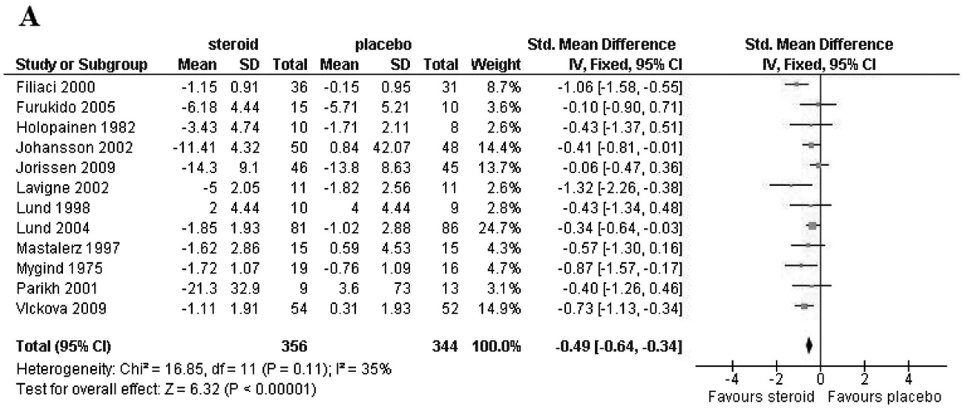

Figure 2. Meta-analysis of topical steroid versus placebo in patients with chronic rhinosinusitis (CRS). (A) symptom improvement; (B) proportion of responders in symptoms.

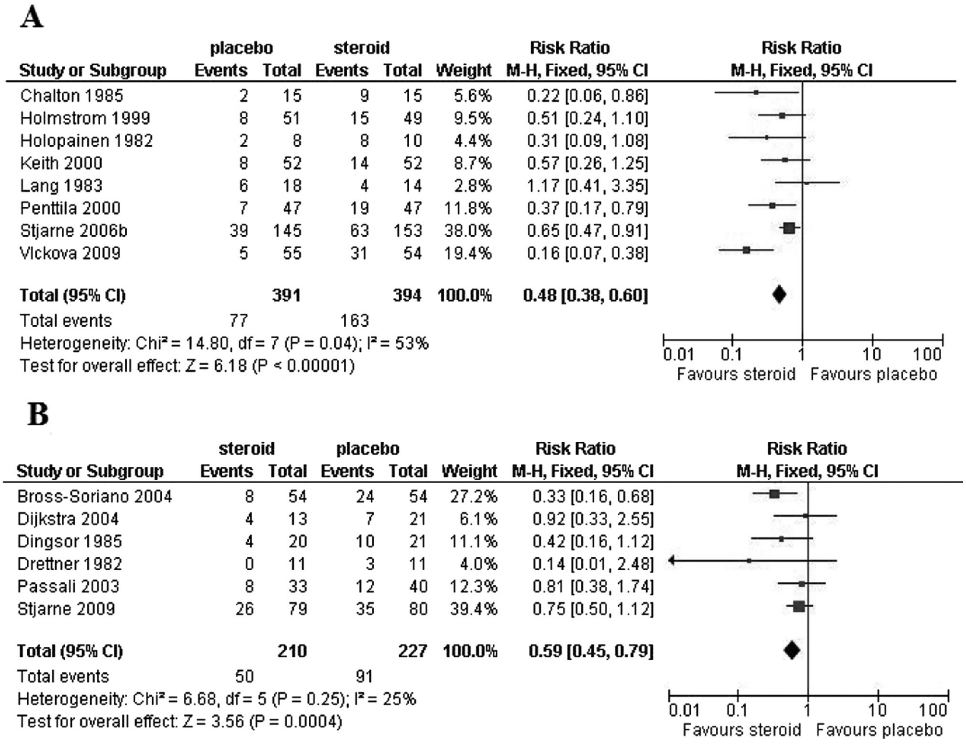

Figure 3. Meta-analysis of topical steroid versus placebo in patients with chronic rhinosinusitis (CRS). (A) proportion of responders in polyp size; (B) polyp recurrence after surgery.

Participants. There were 3961 participants in total. The mean age of the patients was 46.9 years and 63.9% were men.

For 27 trials (56.3%),[17,19,20,26,30,33,34,37–39,43,46–48,50,52–62,64] patients (all or the majority) had sinus surgery before administering steroid either as a cointervention or they had previous surgery documented. In 15 (31.3%) studies,[18,22–25,27–29,31,35,36,44,45,49,51] patients (all or the majority) had no previous sinus surgery. Mixed populations of patients with an undefined proportion having previous surgeries were presented in six trials (12.5%).[32,40–42,63,65]

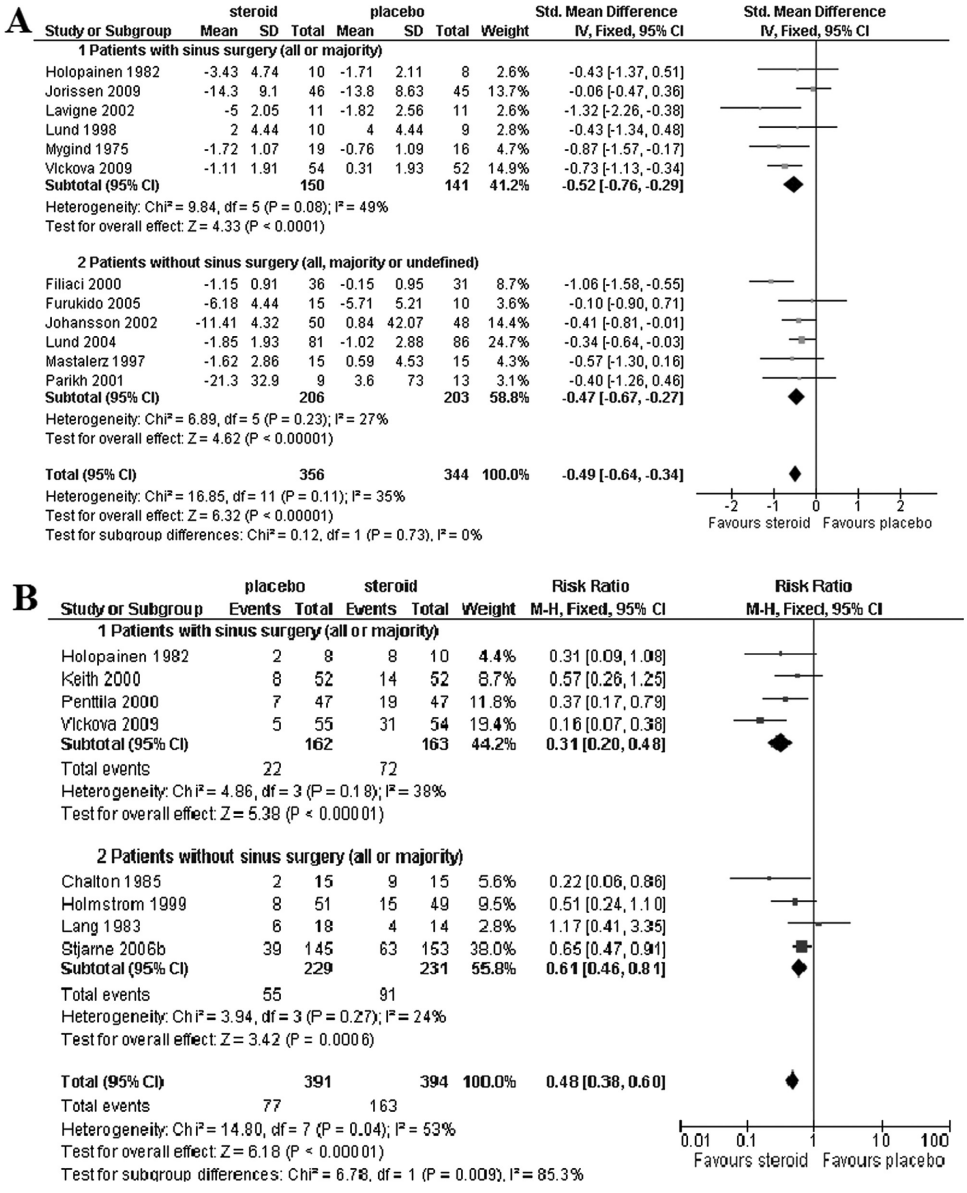

Figure 4. *Subgroup analysis by surgical status in patients with chronic rhinosinusitis (CRS). (A) symptom improvement; (B) proportion of responders in polyp size.*

Interventions. The steroid agents used differed across the studies. They were tixocortol pivalate,[63] fluticasone propionate,[17,19,20,22,26,36,37,41,43,48–50,53,55,56,61] betamethasone,[18,44] beclomethasone dipropionate,[26,43,48,51,52,60,62,65] mometasone furoate,[27–30,38,45,54] budesonide,[23–25,31–35,39,42,57,58,64] flunisolide,[46,47] triamcinolone acetonide,[59] and dexamethasone.[40]

Three trials used a direct sinus delivery technique whereby the drug was instilled directly into the sinus through a sinusotomy tube in one study,[39] intrasinus lavage in one study,[63] and postoperative nasal irrigation in one study.[64]

Thirty trials delivered the topical steroid *via* a nasal spray,[17,22–24,26–30,32,34–38,40,41,43,45–48,51,54,56–58,60,61,65] seven trials used nasal drops,[19,20,44,49,50,53,55] one trial instilled the drug through an intranasal tube,[18] five trials used aerosol,[24,33,42,52,59] three trials used turbuhaler,[25,31,58] and one study[62] used the term "intranasal" without clearly stating the delivery method used.

Outcomes. Forty-one studies (85.4%) of trials reported symptoms as an outcome.[17–20,22–42,45–52,55–59,61,63,65] Symptoms were reported in different ways across studies such as change in symptom scores, combined symptom scores, individual symptom scores, and proportion of responders for particular symptoms.

Thirty studies reported polyp size.[19,20,22–31,33–35,37,44–52,55,56,58,62] These were reported as either change in polyp score, final score at a defined end point, or proportion of responders having a reduction in polyp size. Six studies reported polyp recurrence.[17,30,43,46,47,54] Adverse events were reported in 30 trials.[17,22–34,37–39,45–47,49,50,52,55,57–60,64,65]

Effects of Interventions

When data were pooled for meta-analysis, topical steroids significantly improved overall symptoms when compared with placebo (combined SMD, −0.49; 95% CI, −0.64, −0.34; $p < 0.00001$; 12 trials) and provided a greater proportion of responders in symptom control (RR, 0.59; 95% CI, 0.47, 0.73; $p < 0.00001$; 8 trials; Fig. 2). Both forest plots show low heterogeneity of 35 and 0%, respectively.

Data addressing polyp size were combined in the meta-analysis. The pooled results significantly favored the topical steroid group for the proportion of responders (patients who had a reduction in polyp size; RR, 0.48; 95% CI, 0.38, 0.60; $p < 0.00001$; 8 trials). The I^2 of 53% suggests moderate heterogeneity. Data addressing polyp recurrence after surgery were combined in the meta-analysis with results again significantly favoring the topical steroid group (RR, 0.59; 95% CI, 0.45,

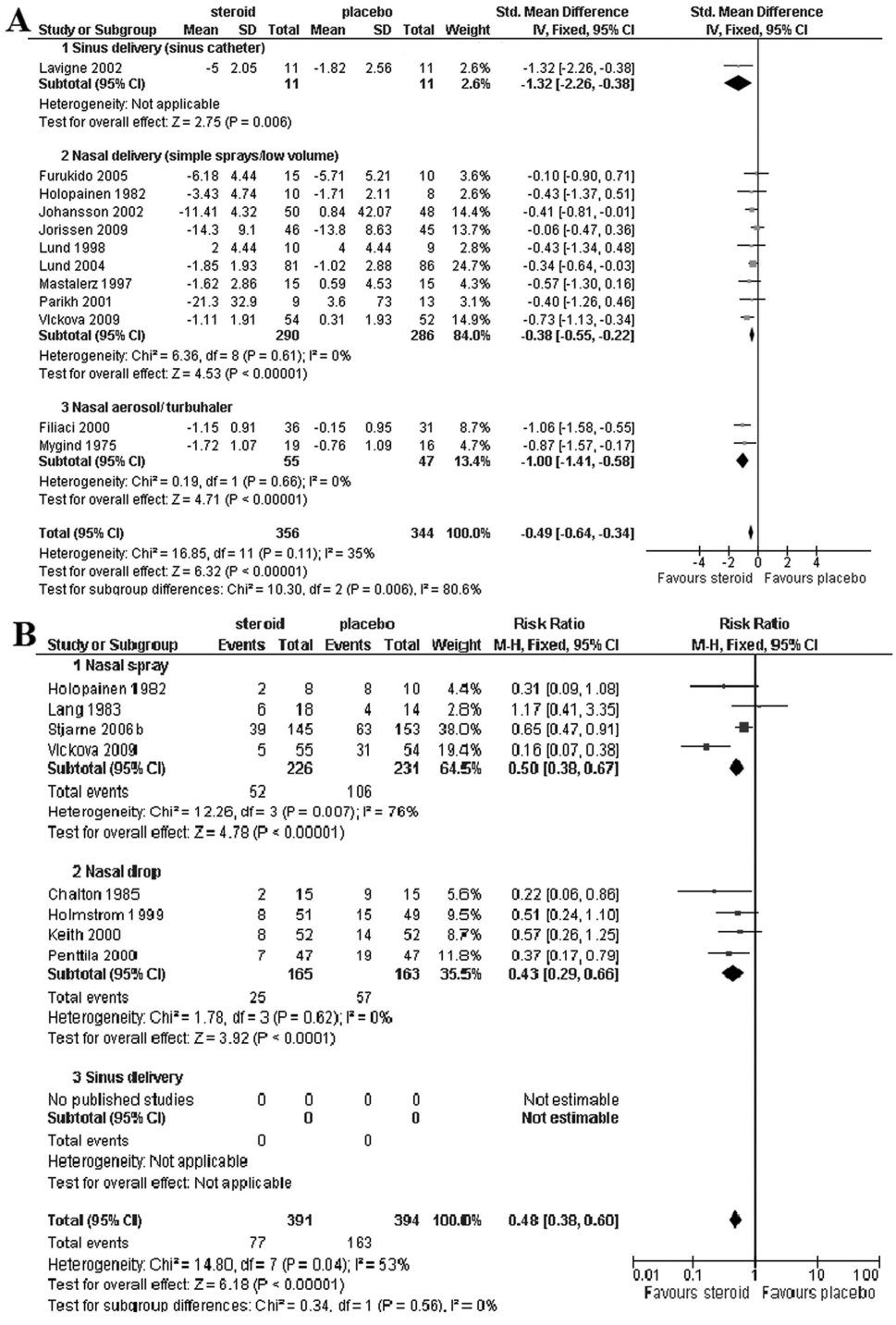

Figure 5. *Subgroup analysis by topical delivery methods in patients with CRSs (A) symptom improvement (B) proportion of responders in polyp size.*

0.79; $p = 0.0004$; 6 trials; Fig. 3). The I^2 of 25% also suggests low heterogeneity.

Subgroup Analysis: Patients with Sinus Surgery versus Patients without Sinus Surgery. Subgroup analyses were performed to explore heterogeneity of symptom improvement (I^2 of 35%) and proportion of responders in polyp size reduction (I^2 of 53%). The beneficial effects of steroid in patients who had received sinus surgery were similar to those without sinus surgery for symptom improvement (SMD, −0.52; 95% CI. −0.76, −0.29 versus SMD, −0.47; 95% CI, −0.67, −0.27; $p = 0.73$). The heterogeneity within subgroups was moderate for patients with surgery ($I^2 = 49\%$) and low for patients without surgery ($I^2 = 27\%$). However, the effect of topical steroid in polyp size reduction was significantly greater in patients with sinus surgery (RR, 0.31; 95% CI, 0.20, 0.48) than those without (RR, 0.61; 95% CI, 0.46, 0.81; $p = 0.009$; Fig. 4). The heterogeneity within subgroups was low ($I^2 = 38$ and 24% for patients with and without surgery).

Subgroup Analysis: By Topical Delivery Methods, Greater symptom improvement could be established when sinus delivery (direct sinus cannulation or postoperative sinonasal irrigation) methods (SMD, −1.32; 95% CI, −2.26, −0.38) were compared with nasal delivery (simple sprays/low volume) methods (SMD, −0.38; 95% CI, −0.55, −0.22; $p < 0.00001$) and nasal aerosol/Turbuhaler (SMD, −1.00; 95%

Table 2 **Adverse events reported in included studies**

Study ID	Steroid Group *n* (%)	Placebo Group *n* (%)	Description of Events Reported	Remarks
Vento 2012[58]	13–17 (43–57)	16–19 (55–63)	Drying, crusting, blood in secretion	No serious events; no differences between treatment groups
Rotenberg[63]	13.4 (2.1)	13.1 (2.8)	12.9 (2.6)	No difference between groups in IOC (intraocular pressure) and adrenocorticotropic hormone levels
Jorissen 2009[37]	29 (63)	28 (62)	Headache, sinusitis, cold	(1) Most common headache; (2) few drug-related events; (3) rare serious events
Dijkstra 2004[17]	NR	NR	Epistaxis	Epistaxis: not higher in steroids group
Lund 2004[31]	39 (48)	46 (53)	Respiratory infection, headache, blood-tinged secretion, viral infection, pharyngitis, sinusitis, flu-like, pain, rhinitis, external ear infection	(1) Most events are mild or moderate; (2) regarding serious events, none were considered to be caused by study medication; (3) no difference of steroids with placebo; (4) no increased incidence of infection
Giger 2003[64]	26* (47) 32# (56)		Epistaxis, dry nose, nasal burning, nasal itching, sinusitis, pharyngitis, otitis, change of taste, eczema, nausea/diarrhea, nasal irritation, common cold	(1) Mild, 61.6%; moderate 4%; severe; 3.8%; (2) most common epistaxis; (3) no candidiasis; (4) no difference between o.d. and b.i.d.; (5) no change in morning serum cortisol level
Lavigne 2002[38]	NR	NR	Tube fell out, epistaxis, diabetes with glycaemia, tube infection, asthma	No sinus irritation from steroid instillation
Chur 2010[44]	NR	NR	NR	There was no difference in 24-hr urinary-free cortisol change in all groups.
Ehnhage 2009[20]	22 (73)	18 (47)	NR	70% Mild; 23% moderate; 7% serious severity
Jankowski 2009[21]	NR	NR	NR	The incidence of AEs was similar in all groups
Stjarne 2009[29]	11 (14)	9 (11)	Epistaxis, dyspepsia, obstruction, headache, sneezing, nausea, nasal congestion, rhinorrhea, skin irritation	Most AE are mild or moderate
Vlckova 2009[36]	13 (24)	11 (20)	Epistaxis	No serious adverse events; morning plasma cortisol was not changed
Stjarne 2006[28]	54 (53)	54 (51)	Respiratory infection, headache, epistaxis	Most AE are mild or moderate
Stjarne 2006[27]	93 (61)	68 (47)	Epistaxis	Most AE are mild or moderate; all epistaxis were mild
Small 2005[26]	56 (49)	64 (55)	Epistaxis and headache	Most AE are mild or moderate and unrelated to study treatment
Jankowski 2001[22]	16 (33)	5 (11)	Blood-tinged nasal secretion, headache, bronchospasm	Most events are mild or moderate
Filiaci 2000[30]	NR	NR	Viral infection, abdominal pain, bronchitis, respiratory infection	80% Are mild to moderate
Keith 2000[49]	12 (23)	9 (17)	Epistaxis, headache, viral respiratory infection	No serious events; no difference between groups in serum cortisol level
Penttila 2000[54]	21 (45)	27 (57)	Respiratory infection, epistaxis	No serious events; no difference in incidence of events between groups
Holmstrom 1999[48]	14 (14)	18 (18)	Epistaxis, throat irritation, nose dryness	There was no change in morning serum cortisol and no difference between treatment groups in the overall frequency of adverse events
Lund 1998[25]	7 (70)	3 (33)	Asthma, respiratory infection, headache	No serious events
Tos 1998[57]	NR	NR	Respiratory infection, nasal mucosal blood, rhinitis, bronchospasm, headache	No serious events
Lildholdt 1995[24]	NR	NR	Epistaxis, dryness	No serious events
Johansen 1993[23]	NR	NR	Dry nose, headache, epistaxis	No differences between treatment groups
Ruhno 1990[56]	6 (33.3)	5 (27.8)	Headache, epistaxis, dizziness	No serious events

Table 2 **Continued**

Study ID	Steroid Group *n* (%)	Placebo Group *n* (%)	Description of Events Reported	Remarks
Hartwig 1988[32]	9 (25)	1 (3)	Nose bleed, nasal irritation	
Dingsor 1985[45]	6 (30)	10 (48)	Itching, sore throat, sneeze, blood traces, nausea	No patients had abnormal plasma cortisol
Drettner 1982[46]	4 (36)	7 (64)	Nasal irritation, blood stain mucus, nasal crust, eye irritation, cataract, pharynx irritation	
Holopainen 1982[33]	NR	NR	Transient nasal stinging and slight throat irritation.	Mean morning plasma cortisol was not different between before and 4 mo after treatment in both groups; local side effects were mild in both groups
Mygind 1975[51]	8 (44)	0 (0)	Nasal infection	

**Beclomethasone dipropionate, 200 μg b.i.d.*
#Beclomethasone dipropionate, 400 μg o.d.
NR = nonreported; AEs = adverse events.

CI, −1.41, −0.58; $p < 0.00001$). Heterogeneity was low ($I^2 = 0\%$) within these subgroups. For the proportion of responders in polyp size reduction, there are no studies using sinus delivery or nasal aerosol/Turbuhaler. No significance difference was found for polyp size reduction between nasal spray (RR, 0.50; 95% CI, 0.38, 0.67) and nasal drops (RR, 0.43; 95% CI, 0.29, 0.66; $p = 0.56$). Heterogeneity was substantial within nasal spray subgroup ($I^2 = 76\%$) but low within nasal drop subgroup ($I^2 = 0\%$; Fig. 5).

Topical Steroid versus No Treatment. Data could not be pooled for meta-analysis from any study. One trial reported symptoms as all groups' symptoms without separate data.[63] Symptoms, polyp size, or polyp recurrence were not reported in one trial.[64] Two trials did not provide standard deviation or any alternative[61,62] and one trial reported University of Pennsylvania Smell Identification Test in each nostril separately.[60]

In summary, for these studies, symptoms[61] ($p < 0.01$), polyp score ($p = 0.003$),[62] and polyp recurrence[61] ($p < 0.01$) were reported as significant improvement in the topical steroid group compared with no intervention. University of Pennsylvania Smell Identification Test was not significantly different between groups[60] ($p = 0.31$). Disease-specific quality of life, endoscopy, and CT score were not significantly different between groups.[64]

Adverse Events. There was no difference between the study group and control in any trial. Most adverse events were mild and moderate. Few were considered to be caused by study medication. The most common event was headache. Data are displayed in Table 2.

DISCUSSION

Topical steroids are beneficial in treating CRS for symptom control, reduction in polyp size, and prevention of polyp recurrence after ESS. The effect for polyp size reduction shows significant heterogeneity between included studies. Subgroup analyses were performed to explore this heterogeneity. One possible explanation is the surgical state of the patient at the time of topical steroid delivery. When this was taken into consideration, greater polyp size reduction was seen in patients having had surgery compared with those without sinus surgery and the heterogeneity in the analysis resolved. There was very little heterogeneity in the studies, all showing reduced polyp recurrence with topical steroids when used in the immediate post-surgical state. The actual surgical state is not often defined and can be variable enough to account for some of the heterogeneity seen.

The heterogeneity was similarly resolved when subgroup analysis by topical delivery methods was performed for symptom improvement. Direct sinus delivery shows significantly better symptom improvement and suggests an attempt at sinus delivery (*c.f.* nasal) with direct sinus mucosa contact is more likely to be effective. Both a wide nasal corridor created by sinus surgery and the methods of topical delivery affect distribution to sinuses and such findings are not surprising.[1,5,7,8] However, there was no clear benefit to symptoms for INCS within the ESS subgroup. On subgroup analysis by sinus surgery for symptom improvement, the heterogeneity was even higher within a "subgroup of patients with sinus surgery." The variability of what actually occurs when surgeons perform ESS is likely to account for the increase in heterogeneity of this "surgery subgroup." There is also variability between different delivery methods in the studies analyzed. Effective sinus distribution requires multiple factors[13] such as positive pressure, large volumes,[66] and various sinus ostial dimensions after ESS.[9] Greatest distribution is likely to be achieved when a wide post-ESS corridor has been created regardless of delivery method.[1,67]

Attempts to examine both variables—the effect of surgery and sinus delivery methods—were performed in two studies. Rotenberg and colleagues[64] reported no difference when budesonide irrigation was compared with a normal saline irrigation. In this study, however, the surgical technique of polypectomy and limited sinus surgery is unlikely to create appropriate access for drug topicalization in a severely affected Samter's triad (asthma, polyps, and aspirin sensitivity) subpopulation. The delivery volume of 60 mL is also inadequate according to data from Buele's study, which proposed using a volume of 100 mL for an effective irrigation.[66] Data were not available for meta-analysis because there was no placebo group as per the other included RCTs. In contrast to the Rotenberg study, Lavigne and colleagues[39] reported positive outcomes when 256 μg of budesonide was administered through a maxillary sinus catheter in postoperative CRS patients. The dosage used is no higher compared with many other studies, but the delivery is guaranteed directly into the sinus through the catheter. Although not a commonly performed delivery technique, it is a controlled method of assessing the effect of the steroid by insuring its delivery to the affected mucosa. Supporting this approach, recent cohort studies of varying eosinophilic CRS subtypes found that postoperative corticosteroid irrigation[1] or placement of steroid-infused carboxymethylcellulose foam[68] improved symptoms and endoscopy findings. Similar findings were seen with large volume irrigations and wide ESS in a cystic fibrosis population.[67] In the postsurgical setting, anatomically directed steroid drops even resulted in a higher percentage of frontal ostia patency when compared with steroid spray,[69] although distribution of simple drops to the remaining sinus cavities remains limited. Unfortunately, no current randomized placebo controlled trial of long duration large volume steroid irrigation post–sinus surgery has been published.

Adverse events reported were often ambiguous. Headache could be drug-related, disease-related, or coincidental. Sinusitis, rhinitis, common cold, and respiratory infection should be considered as disease symptoms rather than adverse events. Epistaxis, dry nose, nasal burning, and nasal irritation are considered to be drug-related events. Minor adverse events from nasal steroid are commonly tolerated by patients. The benefit appears to outweigh the risk.

CONCLUSION

Topical nasal steroids are considered an essential part of the medical treatment of CRS but their effect size is often small. There is consistent evidence, although not comprehensive across all outcomes, that the effects of INCSs are greater when topical steroid is administered after sinus surgery. The impact on polyp reduction was consistent across studies. Attempts at more direct sinus delivery, such as the catheter method, appears to have a greater impact on symptoms.

A well-conducted placebo-controlled randomized trial is required, comparing effective topical drug delivery methods to the sinuses, post–sinus surgery, with an appropriate duration of treatment (preferably 12 months) and using validated outcome measures. RCTs should be preregistered and their reporting should be according to the latest Consolidated Standards of Reporting Trials guidelines.

REFERENCES

1. Snidvongs K, Pratt E, Chin D, et al. Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. Int Forum Allergy Rhinol 2:415–421, 2012.
2. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: Two different approaches to treat nasal polyps. J Allergy Clin Immunol 125:1069–1076, 2010.
3. Harvey RJ, Wallwork BD, and Lund VJ. Anti-inflammatory effects of macrolides: Applications in chronic rhinosinusitis. Immunol Allergy Clin North Am 29:689–703, 2009.
4. Grobler A, Weitzel EK, Buele A, et al. Pre- and postoperative sinus penetration of nasal irrigation. Laryngoscope 118:2078–2081, 2008.
5. Harvey RJ, Goddard JC, Wise SK,and Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. Otolaryngol Head Neck Surg 139:137–142, 2008.
6. Rudmik L, Hoy M, Schlosser RJ, et al. Topical therapies in the management of chronic rhinosinusitis: An evidence-based review with recommendations. Int Forum Allergy Rhinol DOI: 10.1002/alr.21096. (Epub ahead of print) October 8, 2012.
7. Snidvongs K, Chaowanapanja P, Aeumjaturapat S, et al. Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? Am J Rhinol 22:483–486, 2008.
8. Harvey RJ, and Schlosser RJ. Local drug delivery. Otolaryngol Clin North Am 42:829–845, 2009.
9. Singhal D, Weitzel EK, Lin E, et al. Effect of head position and surgical dissection on sinus irrigant penetration in cadavers. Laryngoscope 120:2528–2531, 2010.
10. Brenner PS, Abadie WM, Weitzel EK, et al. Unexpected consequences of transnasal balloon dilation of the maxillary ostium. Int Forum Allergy Rhinol 1:466–470, 2011.
11. Kalish LH, Arendts G, Sacks R, and Craig JC. Topical steroids in chronic rhinosinusitis without polyps: A systematic review and meta-analysis. Otolaryngol Head Neck Surg 141:674–683, 2009.
12. Joe SA, Thambi R, and Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. Otolaryngol Head Neck Surg 139:340–347, 2008.
13. Rudmik L, Schlosser RJ, Smith TL, and Soler ZM. Impact of topical nasal steroid therapy on symptoms of nasal polyposis: A meta-analysis. Laryngoscope 122:1431–1437, 2012.
14. Fokkens W, Lund V, and Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl 20:1–136, 2007.
15. Lanza DC, and Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg 117:S1–S7, 1997.
16. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg 129(suppl):S1–S32, 2003.
17. Dijkstra MD, Ebbens FA, Poublon RM, and Fokkens WJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. Clin Exp Allergy 34:1395–1400, 2004.
18. Furukido K, Takeno S, Ueda T, and Yajin K. Cytokine profile in paranasal effusions in patients with chronic sinusitis using the YAMIK sinus catheter with and without betamethasone. Eur Arch Otorhinolaryngol 262:50–54, 2005.
19. Aukema AA, Mulder PG, and Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. J Allergy Clin Immunol 115: 1017–1023, 2005.
20. Ehnhage A, Olsson P, KölbeckKG, et al. Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. Allergy 64:762–769, 2009.
21. Jankowski R, Klossek JM, Attali V, et al. Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of nasal polyposis. Allergy 64:944–950, 2009.
22. Jankowski R, Schrewelius C, Bonfils P, et al. Efficacy and tolerability of budesonide aqueous nasal spray treatment in patients with nasal polyps. Arch Otolaryngol Head Neck Surg 127:447–452, 2001.
23. VendeloJohansen L, Illum P, Kristensen S, et al. The effect of budesonide (Rhinocort) in the treatment of small and medium-sized nasal polyps. Clin Otolaryngol Allied Sci 18:524–527, 1993.
24. Lildholdt T, Rundcrantz H, and Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: A double-blind, placebo-controlled study of budesonide. Clin Otolaryngol Allied Sci 20:26–30, 1995.
25. Lund VJ, Flood J, Sykes AP, and Richards DH. Effect of fluticasone in severe polyposis. Arch Otolaryngol Head Neck Surg 124:513–518, 1998.
26. Small CB, Hernandez J, Reyes A, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. J Allergy Clin Immunol 116:1275–1281, 2005.
27. StjärneP, Blomgren K, Cayé-Thomasen P, et al. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: A randomized, double-blind, placebo-controlled study. Acta Otolaryngol 126:606–612, 2006.
28. StjärneP, MösgesR, Jorissen M, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. Arch Otolaryngol Head Neck Surg 132:179–185, 2006.
29. StjärneP, Olsson P, and Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg 135:296–302, 2009.
30. Filiaci F, Passali D, Puxeddu R, and Schrewelius C. A randomized controlled trial showing efficacy of once daily intranasal budesonide in nasal polyposis. Rhinology 38:185–190, 2000.
31. Lund VJ, Black JH, Szabo LZ, et al. Efficacy and tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients. Rhinology 42:57–62, 2004.
32. Hartwig S, LindénM, Laurent C, et al. Budesonide nasal spray as prophylactic treatment after polypectomy (a double blind clinical trial). J Laryngol Otol 102:148–151, 1988.
33. Holopainen E, Grahne B, and Malmberg H. Budesonide in the treatment of nasal polyposis. Eur J Resp Dis 63(suppl 122):221–228, 1982.
34. Johansson L, Holmberg K, MelénI, et al. Sensitivity of a new grading system for studying nasal polyps with the potential to detect early changes in polyp size after treatment with a topical corticosteroid (budesonide). Acta Otolaryngol 122:49–53, 2002.
35. Mastalerz L, Milewski M, Duplaga M, et al. Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. Allergy 52:895–900, 1997.
36. Vlckova I, NavrátilP, Kana R, et al. Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device. Rhinology 47:419–426, 2009.
37. Jorissen M, and Bachert C. Effect of corticosteroids on wound healing after endoscopic sinus surgery. Rhinology 47:280–286, 2009.
38. Lavigne F, Cameron L, Renzi PM, et al. Intrasinus administration of topical budesonide to allergic patients with chronic rhinosinusitis following surgery. Laryngoscope 112:858–864, 2002.
39. Sykes DA, Wilson R, Chan KL, et al. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis. A controlled study. Lancet 2:359–360, 1986.
40. Parikh A, Scadding GK, Darby Y, and Baker RC. Topical corticosteroids in chronic rhinosinusitis: A randomized, double-blind, placebo-

controlled trial using fluticasone propionate aqueous nasal spray. Rhinology 39:75–79, 2001.
41. Qvarnberg Y, Kantola O, Salo J, et al. Influence of topical steroid treatment on maxillary sinusitis. Rhinology 30:103–112, 1992.
42. Bross-Soriano D, Arrieta-GómezJR, and Prado-Calleros H. Infections after endoscopic polypectomy using nasal steroids. Otolaryngol Head Neck Surg 130:319–322, 2004.
43. Chalton R, Mackay I, Wilson R, et al. Double blind, placebo controlled trial of betamethasone nasal drops for nasal polyposis. BMJ 291:788, 1985.
44. Chur V, Small CB, Stryszak P, et al. Mometasone furoate nasal spray is safe for the treatment of nasal polyps in pediatric subjects 6–17 years of age. J Allergy Clin Immunol 125:AB101, 2010.
45. DingsørG, Kramer J, Olsholt R, et al. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. Rhinology 23:49–58, 1985.
46. Drettner B, Ebbesen A, and Nilsson M. Prophylactive treatment with flunisolide after polypectomy. Rhinology 20:149–158, 1982.
47. Holmberg K, Juliusson S, Balder B, et al. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. Ann Allergy Asthma Immunol 78:270–276, 1997.
48. Holmstrom M. Clinical performance of fluticasone propionate nasal drops. Allergy Suppl 54:21–25, 1999.
49. Keith P, Nieminen J, Hollingworth K, and Dolovich J. Efficacy and tolerability of fluticasone propionate nasal drops 400 microgram once daily compared with placebo for the treatment of bilateral polyposis in adults. Clin Exp Allergy 30:1460–1468, 2000.
50. Lang DA, and McNeill J. Double blind controlled study of effect of topical steroids on nasal polyps. Clin Otolaryngol 8:135–143, 1983.
51. Mygind N, Pedersen CB, Prytz S, and Sørensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. Clin Allergy 5:159–164, 1975.
52. Olsson P, Ehnhage A, Nordin S, et al. Quality of life is improved by endoscopic surgery and fluticasone in nasal polyposis with asthma. Rhinology 48:325–330, 2010.
53. Passali D, Bernstein JM, Passali FM, et al. Treatment of recurrent chronic hyperplastic sinusitis with nasal polyposis. Arch Otolaryngol Head Neck Surg 129:656–659, 2003.
54. PenttiläM, Poulsen P, Hollingworth K, and Holmström M. Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 microg once daily and twice daily in the treatment of bilateral nasal polyposis: A placebo-controlled randomized study in adult patients. Clin Exp Allergy 30:94–102, 2000.
55. Rowe-Jones JM, Medcalf M, Durham SR, et al. Functional endoscopic sinus surgery: 5 Year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of post-operative fluticasone propionate aqueous nasal spray. Rhinology 43:2–10, 2005.
56. Ruhno J, Andersson B, Denburg J, et al. A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. J Allergy Clin Immunol 86:946–953, 1990.
57. Tos M, Svendstrup F, Arndal H, et al. Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. Am J Rhinol 12:183–189, 1998.
58. Vento SI, Vento K, Blomgren K, et al. Prevention of relapses of nasal polyposis with intranasal triamcinolone acetonide after polyp surgery: A prospective double-blind, placebo-controlled, randomised study with a 9-month follow-up. Clin Otolaryngol 37:117–123, 2012.
59. el Naggar M, Kale S, Aldren C, and Martin F. Effect of Beconase nasal spray on olfactory function in post-nasal polypectomy patients: A prospective controlled trial. J Laryngol Otol 109:941–944, 1995.
60. Jurkiewicz D, Zielnik-Jurkiewicz B, and Wojdas A. Effectiveness of fluticasone propionate in nasal polyps treatment. Int Rev Allergol Clin Immunol 10:22–24, 2004.
61. Karlsson G, and Rundcrantz H. A randomized trial in intranasal beclomethasone dipropionate after polypectomy. Rhinology 20:144–148, 1982.
62. Cuenant G, Stipon JP, Plante-Longchamp G, et al. Efficacy of endonasal neomycin-tixocortol pivalate irrigation in the treatment of chronic allergic and bacterial sinusitis. ORL J Otorhinolaryngol Relat Spec 48:226–232, 1986.
63. Rotenberg BW, Zhang I, Arra I, and Payton KB. Postoperative care for Samter's triad patients undergoing endoscopic sinus surgery: A double-blinded, randomized controlled trial. Laryngoscope 121:2702–2705, 2011.
64. Giger R, Pasche P, Cheseaux C, et al. Comparison of once- versus twice-daily use of beclomethasone dipropionate aqueous nasal spray in the treatment of allergic and non-allergic chronic rhinosinusitis. Eur Arch Otorhinolaryngol 260:135–140, 2003.
65. Beule A, Athanasiadis T, Athanasiadis E, et al. Efficacy of different techniques of sinonasal irrigation after modified Lothrop procedure. Am J Rhinol Allergy 23:85–90, 2009.
66. Virgin FW, Rowe SM, Wade MB, et al. Extensive surgical and comprehensive postoperative medical management for cystic fibrosis chronic rhinosinusitis. Am J Rhinol Allergy 26:70–75, 2012.
67. Pletcher SD, and Goldberg AN. Treatment of recurrent sinonasal polyposis with steroid-infused carboxymethylcellulose foam. Am J Rhinol Allergy 24:451–453, 2010.
68. Hong SD, Jang JY, Kim JH, et al. The effect of anatomically directed topical steroid drops on frontal recess patency after endoscopic sinus surgery: A prospective randomized single blind study. Am J Rhinol Allergy 26:209–212, 2012. □